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POINT PROCESS ALGORITHM FOR THE ESTIMATION OF BI-DIRECTIONAL CARDIORESPIRATORY INTERACTIONS IN PRETERM INFANTS

Selorm Darkey
University of Texas at Tyler

POINT PROCESS ALGORITHM FOR THE ESTIMATION OF BI-DIRECTIONAL CARDIORESPIRATORY INTERACTIONS IN PRETERM INFANTS

by

SELORM K. DARKEY

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SELORM K DARKEY

has been approved for the thesis requirements on
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for the Master of Science in Electrical Engineering

Approvals:

Thesis Chair: Dr. Premananda Indic, Ph.D.

Member: Dr. Mukul Shirvaikar, Ph.D.

Member: Dr. Jimi Francis, Ph.D.

Chair: Dr. Hassan El-Kishky, Ph.D.

FOR JK

Dr. Javier Kypuros, Ph.D.
Dean, College of Engineering.

Dedication

I dedicate this to Almighty God, my parents and all my teachers.

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I am very grateful to God, the Almighty who gave me courage to take up this study.

Thereafter, I am thankful to my supervisor Dr. Premananda Indic for his patience, generous support, encouragement, valuable suggestions and kind supervision. Also, I am grateful to all thesis committee members for taking the time to review my work and their suggestive ideas to make this work a success. Special thanks also to UT Tyler Graduate Fellowship, National Institute of Health Grant U01 HL133536, National Science Foundation and the Smart and Connected Health Grant IIS 166481 for support.

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POINT PROCESS ALGORITHM FOR THE ESTIMATION OF BI-DIRECTIONAL CARDIORESPIRATORY INTERACTIONS IN PRETERM INFANTS.

Selorm K Darkey

Thesis Chair: Premananda Indic, Ph.D.

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Cardiorespiratory interactions tend to be frail in the early stages of life, necessitating the further analysis of their existence since this could turn out to be a significant factor in assessing the neurodevelopment of neonates. Strength of cardio-respiratory interactions are presumed to be weak and rapidly fluctuating in neonates. Even with the extensive significant research that have been dedicated to early human development there still isn't a standard or specific technique to analyze these weak cardio-respiratory fluctuating characteristics in neonates. We employ a mathematical technique that's based on series of tools that have been outstanding in measurement of significant cardio-respiratory control processes in the adult human being. In our case it has been tailored to capture the physiology of the early human cardiovascular system.

We used our technique in the assessment of the cardio-respiratory interactions in 10 preterm infants. The cardio-respiratory interactions were evaluated by employing a specially designed point process model of inter beat interval (RR) of electrocardiogram along with multivariate autoregressive model with respiration as covariate. We computed bi-directional coherence as well as the gain using causal methods between RR and respiration. The technique was used to analyze segments of neonate heart rate during bradycardia (slowness of heart) and segments with regular heart rates, which served as control segments.

Our bivariate model captured the presence significantly high coherence values in the low frequency bands and as well as the bands corresponding to respiratory frequency which indicates

that both the cardiac system and respiration system work together during a bradycardia episode, to resuscitate the neonate from any life-threatening condition.

Our assessment did corroborate the models governing our technique we used in this study and the results established the existence of cardio-respiratory interactions in preterm infants and its influence during a bradycardia event.

CHAPTER 1
INTRODUCTION

Preterm birth falls under the majority causes of death and a notable cause of long-term loss of human potential amongst survivors all around the world. Globally, it was estimated that 1in 10 of all livebirths in are born preterm (i.e. about fifteen million babies born before 37 weeks of gestation), with increasing preterm births in many countries with reliable trend data [1]. A significant issue is that preterm births account for one million deaths yearly, and even the neonates that survive are left with complications like, Bronchopulmonary Dysplasia (BPD), pneumonia, Apnea and bradycardia to name a few [2]. From these reported figures, 75% of these preterm infants could survive death if current cost-effective involvements are made accessible to all. The USA ranks 131st in the world when it comes to preterm birth rates, of which about 1 in 10 babies is delivered preterm in the USA annually [3]. However, it is very important to state that this is a truly global problem, affecting families everywhere far and beyond. Even though a bigger percentage of premature births and related deaths happen in less privileged countries, families in high-income nations are also at risk of having a baby born prematurely [3]. Furthermore, preterm birth can lead to a range of short-term and long-term conditions in survivors, with the degree and severity of unfavorable outcomes rising with decreasing gestational age and decreasing quality of care. Infants who can survive an early birth mostly have breathing problems, cerebral palsy, intellectual disabilities and other lifelong complications [2]. Preterm births tend to be very expensive in terms of immediate neonatal intensive care, babies born just a few weeks early are more likely to be hospitalized and prone to illnesses than full term babies. Preterm infants require ongoing long-term complex health care needs, and when they fail to survive, become lost economic productivity to the society. The Institute of Medicine reports that about $26 billion annually is spent on preterm infants [4]. Preterm birth has a variety of causes and underlying factors usually grouped into spontaneous and provider-initiated preterm births. Although there isn't a clear understanding of the causes of premature birth, in developing countries where there are high rates of infectious diseases, poor overall health and a deficient health care system, a woman is at a higher risk of preterm labor as compared to those in higher income countries. Other few known causes or premature births have been known to include low or high maternal age

(usually below 18 or above 39), multiple miscarriages, carrying of multiple fetuses or even structural abnormalities of the womb [5]. A constant recording of all pregnancy outcomes, including stillbirths and standard application of preterm definitions is noteworthy in all situations to advance in both the understanding and the monitoring of trends. Context specific innovative solutions are urgently needed to prevent birth and hence reduce deaths in preterm infants. These efforts must be coupled with immediate action to implement improved antenatal and new born care to increase survival and reduce disability amongst preterm infants [6].

1.1 PREMATURITY

Prematurity is when infants are born earlier than the expected duration for gestation this is usually known to occur 3 weeks before the expected due date [5-6]. Preterm infants, more specifically those delivered early, frequently tend to have health complications. Generally, these complications vary, but the earlier the child is born the higher the risk of complications. Prematurity has been divided into four groups [5];

- **Late preterm** (i.e. baby is born between 34 and 36 completed weeks of pregnancy),
- **Moderately preterm** (i.e. baby born between 32 and 34 of pregnancy),
- **Very preterm** (i.e. born at less than 32 of pregnancy),
- **Extremely preterm** (i.e. born at or before 25 weeks of pregnancy.

These preterm infants also show symptoms to indicate prematurity. These symptoms vary but to mention a few;

- Preterm infants exhibit respiratory distress (labored breathing).
- They have low body temperature, due to a lack of stored body fat.
- They have a small body size accompanied with a disproportionately huge head.
- They have no reflexes for sucking and swallowing which then makes it difficult to feed

As has been mentioned earlier the main cause of premature birth is still not clear. Nonetheless, there are individual practices that put mothers at the risk of having to deliver prematurely;

- Smoking of cigarettes and use of illicit drugs.
- Giving birth in short intervals, an interval less than six months between pregnancy.

- Conditions such as high blood pressure and diabetes.
- Being underweight or obese before pregnancy [5].

1.1.2 COMPLICATIONS OF PREMATURITY

Premature infants require a lot care as well as support to survive and hence are admitted to the NICU for observation and the appropriate treatment. These preterm infants are risk of experiencing short-term and long-term complications since most of their organs are not fully matured to carry out their specific functions without support. We will discuss briefly a few short-term and long-term adverse outcomes of preterm births.

Short term outcomes:

Apnea:

This In a lung disorder which occurs due to the immaturity of the infant's respiratory system hence making breathing difficult. During apnea, the infant experiences short term cessation in breathing. Apnea tends to last for a duration of 10 seconds or longer, it is sometimes accompanied by bradycardia. Apnea usually occur during sleep hence the name sleep apnea. There are 3 types of apnea that have been observed in preterm infants, central, obstructive and mixed [2].

Bradycardia:

A medical condition in preterm infants where the heart rate is significantly low is known as Bradycardia. The mean heart rate (HR) of premature infants is 120-180 beats per minute (bpm). A heart rate less than 100 bpm [NB: mild bradycardia (100-80 bpm), moderate (80-60 bpm), and severe (<60 bpm)] [4] would end up in a depletion in cerebral blood velocities from baseline. This in effect may have adverse effect on preterm infants [5].

Hypoxia:

It is a condition where insufficient amount of oxygen reaches the body or a part of the body (tissue hypoxia). Hypoxia is known to be a common cause of brain damage in neonates [7].

Brain Problems:

The more premature the infant (i.e. the earlier it is born), the higher the possibility of bleeding in the brain, this a condition widely known as intraventricular hemorrhage. In most cases these hemorrhages are mild and resolve with little short-term effect. But there can also be cases with large brain bleeding which leave the infant with permanent brain injury [2].

Long-term complications:

Cerebral Palsy:

This is a complication with the infant's muscle tone, movement or posture that usually occurs by infections, injury to the child's maturing brain or inadequate blood flow. This may happen at the time of pregnancy or while the infant is newly born and immature [5].

Vision impairments:

Preterm infants are at risk of suffering long term vision impairments, an example of such a condition is retinopathy of prematurity. This condition happens when the blood vessels swell and overgrow in the light-sensitive layer of nerves in the retina, hence forcing it out of position. When the retina is detached from the back, it's a condition known as retinal detachment. If this goes unnoticed can impair vision and cause blindness [5].

Its however important to note that not all adverse outcomes are mentioned here.

1.3 LIFE IN THE NICU:

Most of the time, after a preterm infant is born, they are admitted to the NICU. Here, uninterrupted specialized care is administered by the neonatal physicians and nurses to observe and treat the complications due to prematurity. The NICU is made up of four levels according to required attention by a preterm infant [8-9].

- Level I gives basic care to newborns.
- Level II is made up of a Special Care Nursery to give care to preterm infants older 32 weeks through CPAP (Continuous Positive Airway Pressure), mechanical ventilation for up to 24 hours.

- Level III Neonatal Intensive comprises of a comprehensive care with high frequency ventilation and an on-site accessibility to pediatric subspecialists.
- Level IV is the regionalized neonatal intensive care unit, it provides level III care also provides extracorporeal membrane oxygenation (ECMO) therapy is has been designed and equipped to treat complex cardiac abnormalities that may require cardiopulmonary bypass [9].

In NICUs physicians are faced with challenging task of analyzing the risk of discharging infants based on their external physiological developmental features. Extremely preterm infants are usually treated for about 71 days in the NICU, very preterm infants are taken care of for about 40 days in the NICU. Moderately preterm infants and late preterm infants spend averagely 12 days and 4 days respectively, in the NICU [6].

With a better understanding of cardiorespiratory coupling in preterm infants, the challenging task NICU physician must deal with when discharging preterm infants will be mitigated. This is because the internal physiological mechanism of these systems (cardiac system and respiratory system) will be captured and interpreted reliably enough to understand the health status of an infant before being released from the NICU. The prediction of this coupling could be important to aid NICU physicians to determine when it is safe to discharge infants from the NICU as well have a fair idea of their growth process since it has always been a tough task in figuring out the risks of these babies based on their physiological signals.

In this thesis, we focused on studying the interactions between the cardiac system and respiratory system in preterm infants, these respiratory and cardiac signals are monitored closely to establish if there is any sort of coupling and if there is what direction the coupling takes. (i.e. if the respiratory system influences the cardiac system or vice versa). Cardiorespiratory interaction is an important marker in assessing the neurodevelopment of neonates. A reliable estimation of such interactions can help clinicians to get an insight into neonatal health and subsequent development.

The next chapter will give an insight on previous research works in this sector relating to our current research.

CHAPTER 2
BACKGROUND

It is a current notion that organs influence one another by extracellular signaling or through nervous system. Uncoupling (i.e. a disruption in the communicating structure that exists between systems) may occur when illnesses of different sorts tend to disturb this complex, finely functional system. If organs exhibit an obvious oscillatory dynamic, then It is said to be an indication of great health. Cardiorespiratory coupling is a result of composite central and involuntary nervous system processes [10].

Cardiorespiratory interactions are frail at the premature levels of human growth, meaning that analysis of their existence and authenticity may be vital in determining the maturity in infants [11]. In the past decades, understanding about interactions that link respiratory system to the cardiovascular systems has slowly advanced with random reports of analysis on the relationships of biological patterns and the central nervous system functionality. Biological patterns corresponding with secondary involuntary system functionality, conversely, have been comprehensively investigated [12]. Neural systems are known to modulate cardiovascular indicators, for example arterial blood pressure (ABP) and heart rate variability (HR) together with respiratory indicators, like inter-breath interval (IBI) series [12]. Detectable instances of these kind of interactions are respiratory sinus arrhythmia (RSA) and cardio-ventilatory interaction. Respiratory sinus arrhythmia (RSA) is the increase and decrease of heart variability with respiration controlled by the baroreflex, respiratory gating, or both. The existence RSA represents a good outcome in several clinical cases, including intensive care [10]. RSA generation can be related mainly to direct brainstem control of the cardiac vagal preganglionic neurons and by restriction of cardiac vagal efferent activity by lung inflation. RSA is also believed to improve pulmonary gas exchange [12]. Heart rate variability (HRV) is a significant measure of cardiovascular state. In healthy adults, heart rate typically rises with inspiration and falls with expiration. Adults have a breathing model with a mean respiratory rate of roughly 12 breaths per minute (0.2 Hz) and, assuming a linear pattern, these oscillations directly reflect the variability of the heartbeat. The RSA is observed as a peak in the HRV spectrum in the normal respiratory frequency range. A well-defined peak in the HRV spectrum representing RSA denotes the existence of cardio-respiratory coupling in adults. Despite the fact that the exact relationship

between HRV and respiration in preterm infants remains incomplete, the regular respiratory rate of infants is approximately 60 breathes per minute (1Hz). Nevertheless, majority of preterm infants experience irregular breathing patterns with recurrent breathing and brief breaks in breathing (apnea) that results in frequencies lower than the normal range. Hence, the respiratory influence on the heart rate, should there be any, will be exist at different ranges of frequencies, below 1 Hz. Due to this, in preterm infants, the normal RSA, (i.e. the peak in the power spectrum of HRV at the normal breathing frequency of ~ 1Hz) may not be noticed in the HRV spectrum as a result of the inconsistency in breathing. An extra possible difficulty in relying on traditional spectral analysis is that heart rate fluctuations maybe present at the respiratory frequencies even during the nonexistence of respiration [11].

A lot of studies explain cardiorespiratory interaction as a connection/communication present linking two subsystems that could be likened to two weakly coupled oscillators. The primary idea is that supposing we have two feebly linked systems, the magnitude of these systems' oscillations may have no correlation whereas the phases of systems do mutually unsettle each other. After establishing this notion, it is reasonable to use the method of a phase analysis of RR series and respiratory signal to look into cardiorespiratory synchronization alternately to utilizing a classical amplitude assessment method. The characteristics of the cardiorespiratory system can be thought of the systems working together, implying a multi-stable system swapping between numerous phase attractive maps, accompanied by a precedence for a certain type of phase relations, which may be thought of as attracting frequency correlations. These various means of interactions are not independent of each other, rather they may concurrently exist side-by-side, depicting numerous characteristics of neural setting and acting on varying time intervals [12].

2.1 LITERATURE SURVEY

As stated earlier this chapter assesses previous research studies that have be conducted in relation to cardiorespiratory interactions, considering from conventional to more advanced signal-processing techniques, such as point process analysis, phase locking analysis, and other advanced signal processing techniques. However, these linear and non-linear methods give estimates of symmetric interaction and are deficient within the capability to assess possible various causal procedures that may control cardiorespiratory characteristics.

2.1.2 CARDIORESPIRATORY INTERACTIONS LITERATURE SURVEY

Lucchini and co. [12] suggested a methodological approach that measures the phase coupling and its directionality in a populace of newly born babies born ranging from 35 and 40 weeks of (GA) (late preterm). The main idea was to evaluate if GA (gestational age) at birth has a significant influence on the evolution of phase synchronization and the directionality of the coupling that occurs connecting the functionality of both the cardiovascular system and respiratory system. The infant dataset included 273 babies delivered at Morgan Stanley Children's Hospital of New York with gestational ages ranging from 35 and 40 weeks. The ECG signals were recorded at 500Hz whereas respiration signals were obtained at 200Hz. The heart beat waves (R peaks) observed on the electrocardiogram was made possible by using a software built on the Pan-Tompkins algorithm. The R peaks obtained were then analyzed optically. At (0.05-3.5 Hz) the respiration signal was filtered. The acceptance thresholds for the RR interval was placed between a range from 0.3-0.667s, accompanied by a fluctuation that occurred at consecutive RR intervals of 10%, whereas thresholds for respiration was at 0.51-2.51 s and an outright 40% change. With a Savitzky-Golay filter the respiratory signal was filtered and detrended the instantaneous phase evaluated by functions provided by the data analysis with model of coupled oscillators (DAMOCO) toolbox). The Hilbert transform was used to calculate the respiration signal protophase, while with right transformation of protophase the phase is obtained. At 200Hz phases of electrocardiogram and respiration were sampled again to get two synchronous phase series. The method of the synchronization index λ was the choice used to measure the level of synchronization, due to its well-known reliability. The estimation of the magnitude of synchronization is by employing the λ index implied that the phases of the RR and respiration were deemed as cyclic($\mathrm{mod}2\pi$).

During this study, the evolution map approach (EMA) algorithm was employed because it has the capability of achieving unsymmetrical directionality stability from short noisy records and quantifies which of the systems is under assessment is influencing it is other counterparts the more. Results from the study showed unalike directionality profile as a function of gestational age and sleep state.it was concluded that babies born even only between a week and 4 weeks early may exhibit inconsistent cardiorespiratory characteristics in comparison to the full term, hinting an important role for the last weeks of pregnancy in the development of the coupling between the

cardiovascular and the respiratory systems. Furthermore, the suggested findings of cardiorespiratory coupling from this study could serve as a tool evaluate development of cardiorespiratory regulation, hence going on to serve as a biological marker in risk stratification [12].

Clark and co. [10] to understand a breath-by-breath assessment of cardiorespiratory coupling the study utilized the phase- based approach. The findings of this cardiorespiratory interaction did not clarify whether the cardiac system's control of respiration was related to cardio-ventilatory coupling and whether respiratory effects on heart rate was connected with RSA (respiratory sinus arrhythmia). The study was carried out by firstly analyzing 18 infant-years of data which was collected from 1,202 patients in the NICU at University of Virginia. Proof of interaction was recorded in 3.3 patient years of the data (i.e. 18%). The wave forms were then analyzed in 3 steps: breath and QRS detection, measurement of cardiorespiratory interaction and noise quantification. The noise quantification was carried out by the addition of clinically approved frequency content noise to the noise-free waveforms and going on to calculate the signal quality indexes. The signal quality indexes were examined as a function of added noise and constricted subsequent evaluation on signals with low approximated noise levels. The EKG lead with the least noise automatically detected the QRS complexes using 3 detection algorithms. The first algorithm is threshold-based algorithm that was enacted by Clifford and coworkers. The second algorithm was used to take out the T- and P- waves by utilizing a high-pass filter. The last algorithm was used to decompose the EKG signal employing a continuous Haar wavelet transform scales 2^n where $n=1,2...5$. Complexes that were identified by the mentioned methods shown as kernels of unit height and width of 80ms at 3 standard deviations.

To evaluate cardiac reliance on respiration, they evaluated temporal relation of heart beats occurring within the respiratory phase. Every heartbeat was numbered according to the respiration phase in which it occurred. Communication of the heart to the lung which results in the restricting of heartbeats within respiratory cycle which was noticeable in probability densities. To measure the range of confinement of heartbeats within a respiratory phase They used Shannon Entropy S, of the probability densities. Thus, meaning that lower the values of entropy the more restriction of heartbeats within a respiratory phase, implying more interplay. The study found that, cardiorespiratory interaction increased with maturity, but the rate of rise was independent of GA

at birth. There was evidence of a slight correlation between this quantification of cardiorespiratory interaction and cardio-ventilatory coupling with no proof of RSA. The study suggested the need for further investigation of this mechanism [10].

Indic and co. [11] performed an evaluation of cardio respiratory interactions present in preterm babies utilizing a bivariate autoregressive modeling and surrogate data analysis. This approach was used to study the cardio-respiratory reactions in 11 preterm infants. The study was performed in 3 steps, data preprocessing, time domain analysis, frequency domain analysis and surrogate data analysis. The dataset used in this analysis were from experimental protocol designed to assess the aftereffect of mild vibrotactile stimulation in preterm infants. The electrocardiogram signals were sampled at a rate of 200 Hz. Abdominal respiratory movements were also sampled at a rate of 100 Hz using a respiratory Inductance plethysmograph.

The peak to peak (RR) series were optically looked over and amended of any errors. The R-waves were identified by employing a derivative and threshold algorithm. To get a better recognition of the signals, they used a fourth order band-pass zero-phase Butter-worth filter. The RR series recorded are then interpolated and re-sampled at 3 Hz with their corresponding respiratory signals. A standard approach was used to evaluate the time domain measurements. To record the frequency domain measures, the respiration together with the RR were assumed to be the output variables of a multivariate autoregressive model.

The coefficients of the model were calculated by solving the extended Yule-Walker equations and auto-spectra. The gain and coherence were obtained in the frequency domain from the calculated coefficients. This approach ultimately gives an assessment of a linear relationship between the RR and respiration as well as its importance, defined along the range of frequencies. The last task performed was the surrogate data analysis, this was simply done by performing the methods used for the original signals on a generated surrogate series. The multivariate assessment unveiled an appreciably greater coherence, as established by surrogate data analysis, in the frequency range related with eupneic breathing in comparison to the other ranges. The analysis done in this study confirmed the models backing their approach, and the results indicated the presence of cardiorespiratory coupling in early stages of maturity. More importantly during moments of mild mechanosensory intervention, hence hinting for further application of this method [11].

Yoon and co. [13] investigated directional coupling present cardiorespiratory interactions in the various physiological states (i.e. sleep stages) and conditions. The main sleep condition considered in this study was obstructive sleep apnea OSA. The study was conducted in 3 steps; data collection, data processing and directionality analysis. Data was collected from 39 healthy patients, 24 patients with mild OSA, 21 patients with moderate OSA and 23 patients with severe OSA. The heartbeats from these patients were recorded from an electrocardiogram whereas the respiratory efforts were collected from a polysomnographic data of the patients. The directionality assessment was executed by utilizing the evolution map approach. They modified the DAMOCO (MATLAB toolbox for multivariate data analysis based on coupled oscillators approach version1.0) to suit the aim of the study, this was then used to obtain the directionality index. Weak and strong interactions of the cardiorespiratory system was affirmed by using the mean phase coherence. During moments of wakefulness (mean value of -0.61) and restless sleep (-0.55) it was observed that the unidirectional coupling from the respiratory to the cardiac system rises. Additionally, this observed unidirectional coupling in the cardiorespiratory systems was seen to decrease appreciably during moments of light sleep (-0.52) and in deep sleep. During deep sleep this unidirectional coupling decrease further moving towards becoming a bidirectional coupling. Furthermore, this unidirectional coupling of this cardiorespiratory systems seems to increase significantly according to severity of obstructive sleep apnea (OSA). The study went on to conclude that, the involuntary nervous control of these individual systems may be linked to the varying coupling characteristics in the different conditions and states[13].

Kontaxis and co. [14] analyzed the quadratic phase coupling present between heart rate and respiration. It was done with a variety of methods, firstly by a suggested approach to detect QPC (quadratic phase coupling), this method is known as the real wavelet biphase (RWB). A method suggested after this first procedure is one for QPC measurement known as the normalized wavelet biamplitude. In order to tryout the dependability of the real wavelet biphase (RWB) in detecting quadratic phase coupling (QPC), they performed a simulation study. This reliability test was also carried out to confirm if the RWB could still detect the QPC in the instance of consistent delays between interacting oscillations and could differentiate the QPC from quadratic phase uncoupling. Finally, A tilt-table protocol set up consisting of 17 young healthful patients, was used to study quadratic cardiorespiratory couplings. The results from the simulated study went on to establish that the RWB can identify even frail QPC with delays in the set time space, which happens to be

a normal situation in the involuntary nervous system modulation of the heart rate. With the head up tilt position compared to the supine position, it was observed that there was an appreciable reduction of NWB between low and high frequencies of HRV and respiration per the results obtained from the database.

This study concluded that, the applied methods did identify and measure resolutely QPC and trail the interaction between respiration and various HRV elements during involuntary nervous system changes. This approach can also aid in analyzing changes of nonlinear cardiorespiratory coupling linked involuntary nervous system dysfunction and physiological managing of HRV in cardiovascular ailments [14].

2.1.3 POINT PROCESS LITERATURE SURVEY

In this thesis we employ a point process model (PPM) to analyze the cardio-respiratory variables in preterm infants. This is a statistical representation of a batch of mathematical points haphazardly distributed in a mathematical space such the cartesian plane. This is a statistical tool employed for analyzing spatial datasets in a wide range of discipline such as economics, astronomy and others [15]. For the rest of this section we look at some previous research works that employed the point process model in their analysis.

Gee and co. [16] improved heart rate estimation in premature babies by using a bivariate point process investigation of heart rate and respiration. Readings were taken by randomly selecting 10 preterm infants who were breathing room air. The mean post conceptual age was 31.14 weeks with an average weight of 1468grams. The ECG signals were collected and at a sampling rate of 500Hz and recorded through a time span of approximately 20-70 hours. The respiration signal was recorded at 50Hz by a respiratory inductance plethysmography during abdominal inspiration and exhalation movements. An altered Pan-Tomkins peak detection algorithm is used to produce peak-to-peak R-R intervals from the electrocardiogram signal. The study went on to analyze sections of the data with normal heart rates and clinical bradycardias, 30 severe bradycardias were spontaneously selected. All this investigation was performed on the 3-minute window just before the occurrence of bradycardia event. The study hypothesized that the approximation of heart rate can be enhanced by involving respiration as a state variable. And this should depend on the structure that governs cardio-respiratory coherence. For the dataset, the study was able to show

that involving respiration as a covariate betters the approximation precision by a mean of 11% over bradycardia severity and lessens the maximum error by 8%. The study also went on to find that cardio-respiratory coherence was more significant in low frequency content just before the occurrence of severe bradycardia. Meaning, including respiratory details can enhance the models of heart rate dynamics and zero in on inherent features for predicting bradycardia [16].

Barbieri and co. [17] used time-variant bivariate spectral analysis for continuous quantification of respiratory and baroreflex control of heart rate. Lately, various digital signal processing methods have been employed in analyzing the complicated interactions and structures that come into play to control the cardiovascular system. In spite of the significant progress that has been made in this field, a precise and continuous quantitative assessment of this involuntary system state is still yet to be established. This study tackles mainly, models that can take into consideration the closed-loop style of the interactivity between system inputs and outputs. Secondly, to come up with possibility of obtaining near-continuous analysis of the parameters of these methods so that they can be applicable in clinical medicine if necessary. The interactive communication that is present between arterial blood pressure (ABP), heart rate and respiration can be represented by parametric bivariate models. In the study, to enhance the recognition of respiratory influence on HR (RSA, respiratory sinus arrythmia), ABP influence on HR (baroreflex), the frequency content of respiration and ABP are widened. A bivariate autoregressive time-variant model was employed to recognize the characteristic HR and ABP spectral variables of LF (low frequency) and HF (high frequency) power, and the ratio LF/HF. Furthermore, cross-variables namely LF and HF gain for ABP-HR, coherent power and RSA gain were calculated. Alike outcomes were attained using a "batch" algorithm, but the time-variant approach produce almost continuous parameters, making it possible to monitor or observe circulatory control in real-time continuously [17].

Kodituwakku and co. [18] applied a point process time-frequency assessment to respiratory sinus arrythmia under altered respiration dynamics. The study suggested an algorithm to measure rapid RSA as applied to heart beat intervals with respiratory readings under changing respiration states. An inverse gaussian point process is modeled from the pulse interval (PI), a bivariate regression is modeled from the instantaneous mean PI including both past PI and respiration readings recorded at the respective beats. To calculate the model variables, a point process maximum likelihood algorithm is employed. A frequency domain transfer function method is used measure

the instantaneous RSA. A Kolmogorov-Smirnov goodness-of-fit assessment was used to verify the model statistically. The results of this study showed that the algorithm was capable of tracking significant changes in cardiorespiratory interactivity during triggered meditation, apart from that not observed in control resting conditions [18].

Chapter 3
METHODS

This section will entail a detailed description of procedures undertaken to achieve the results of this study. It includes a description of the preterm infant data acquisition, the generation of the waveforms from the dataset, the mathematical theory governing the point process algorithm used in the study. Point process model of RR with respiration as covariate was used to quantify the cardiorespiratory interactions in preterm infants. The Kolmogorov-Smirnov statistic was then used to evaluate the goodness-of-fit of the proposed point process model.

3.1 DATA COLLECTION

The preterm infant data was obtained from physionet.org under the Preterm Infant Cardio-Respiratory Signals database (PICS), which was previously in developing algorithms for the prediction of life-threatening events in preterm infants by Gee and co. [16]. The data comprises ECG and respiration readings of 10 preterm babies obtained from the Neonatal Intensive Care Unit (NICU) of the University of Massachusetts Memorial Healthcare. In this work all 10 infants were studied, with a post-conceptual mean age of 31.4 weeks and mean weight of 1468 grams. A 3-lead ECG of a single channel signal which readings were taken at 500Hz (when feasible) from patient monitors (i.e. Intellivue MP70) for a duration of about 20-70 hours for each preterm baby. In the instance where there was no available ECG channel, a compound ECG signal reading taken at 250Hz was employed. This option of ECG availability was as result of nursing preference, hence researchers had no influence on the signals that displayed on the MP70 monitors. Using external inductance bands attached to areas around the chest walls and abdomen the respiration signals were recorded at 50Hz and synchronized using VueLogger. (A Wyss Institute, Harvard University data acquisition system).[19]

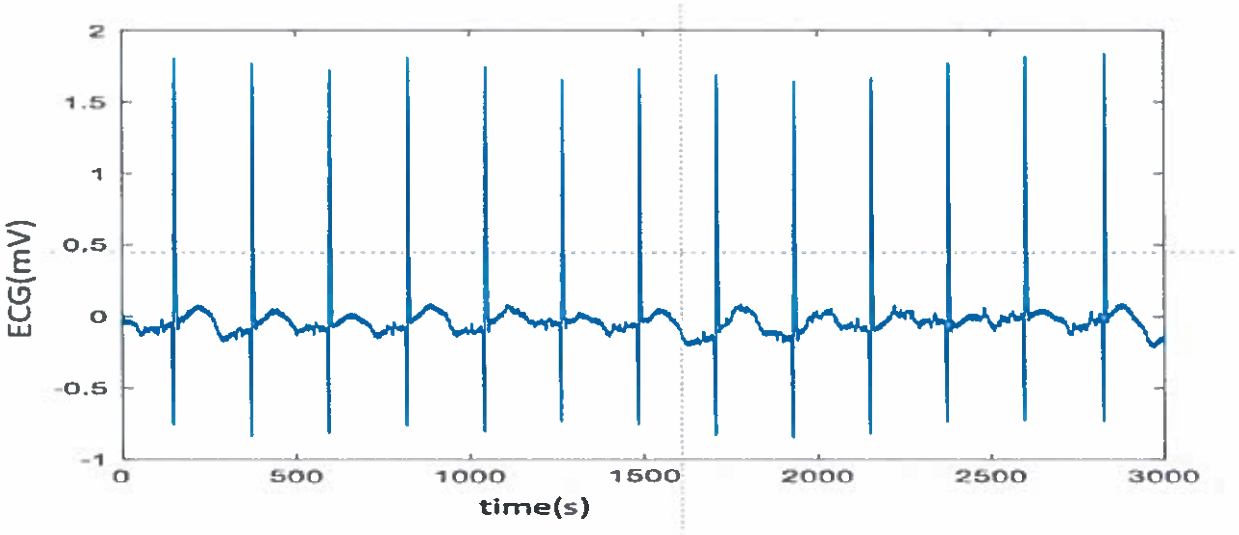

Figure 1 An example of ECG signal of one of the preterm infants in this study. The peak of the ECG signal (R-wave) is considered as a point event.

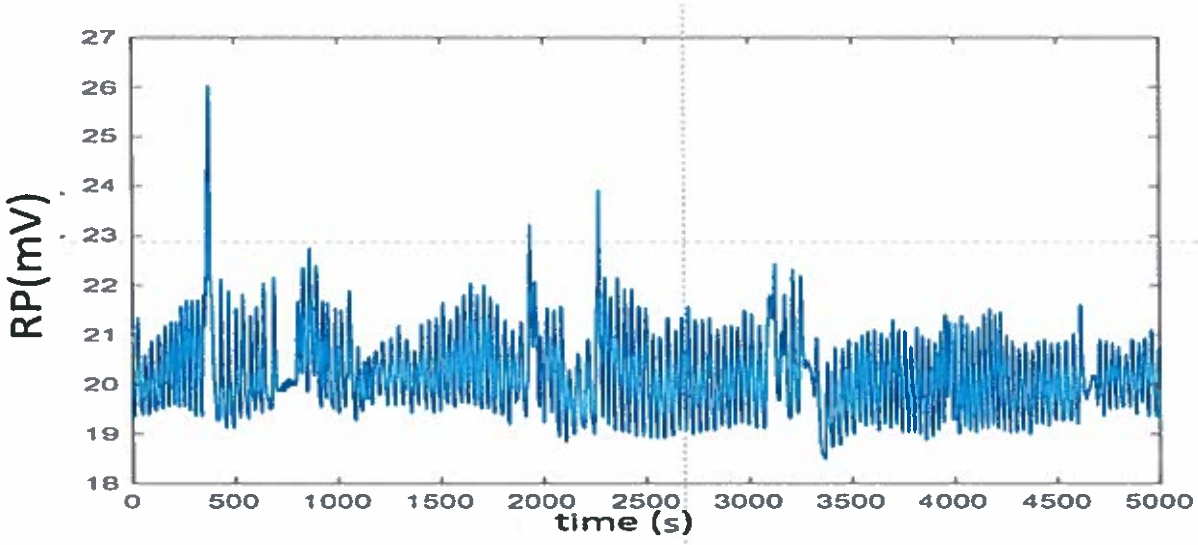

Figure.2 A respiration waveform of the same preterm infant presented in Figure 3.1 corresponding to the same time duration. The respiratory signal shows instability in breathing which is typical for preterm infants.

3.2 DETERMINATION OF R-R INTERVAL

The single channel ECG and Respiration readings are made available on the physionet website in WFDB format [20]. This means a WFDB tool box is required to extract the waveform from the physionet data. This was done by downloading and incorporating the WFDB toolbox in MATLAB to facilitate the extraction of both the ECG and respiration waveforms from the downloaded physionet data. It is also important to note that ECG readings were taken at 500HZ (sampling frequency) with the exception of infants 1 and 5, they had their compound ECG signal sampled at 250Hz. After using WFDB toolbox in MATLAB to generate the ECG waveforms a modified version of a Pan-Tomkins peak detection algorithms is used to extract the R-R peak intervals. A visual inspection is performed on the annotations to take out any artifacts due to movement, erroneous peak detection and disconnection.

There were 10 infants which were marked as infant 1 to infant 10. For infant 1, respiration was sampled at 500Hz, the other infants had their respiration signals sampled at 50Hz. The abdomen inductance band information was not available for infant 1 at the time of study hence the respiration signal reading was taken by using the respiration signal from the MP70 [19]. The peaks of the respiration were extracted with an algorithm and the annotations not vetted yet. With the data and waveforms of the R-R intervals and respiration extracted, an algorithm to relate every peak in the R-R waveform to its corresponding respiration value. The value of the respiratory signal at the corresponding peak of the ECG signal was determined by interpolating the respiration at the timing of those peaks with the sampled respiratory values before and after the timing of the peak.

With the generated peak-to-peak R-R series from the ECG signal, segments including normal heart rates (i.e. >100 beats per min) and bradycardias: severe (i.e. <60 beats per min), moderate (i.e. 80-60 beats per min) and mild (i.e. 100-80 beats per min) were investigated [19]. Out of the dataset 126 events of bradycardias, approximately 12 events per infant, were noted. All analyzed segments are on the 10-minute window prior to each bradycardia event as well as 10-minute window after the event. In this study, we combined any bradycardia event within the 10-minute windows leading to a bradycardia or after a bradycardia has occurred to prevent or minimize statistical distortions during the estimation phase.

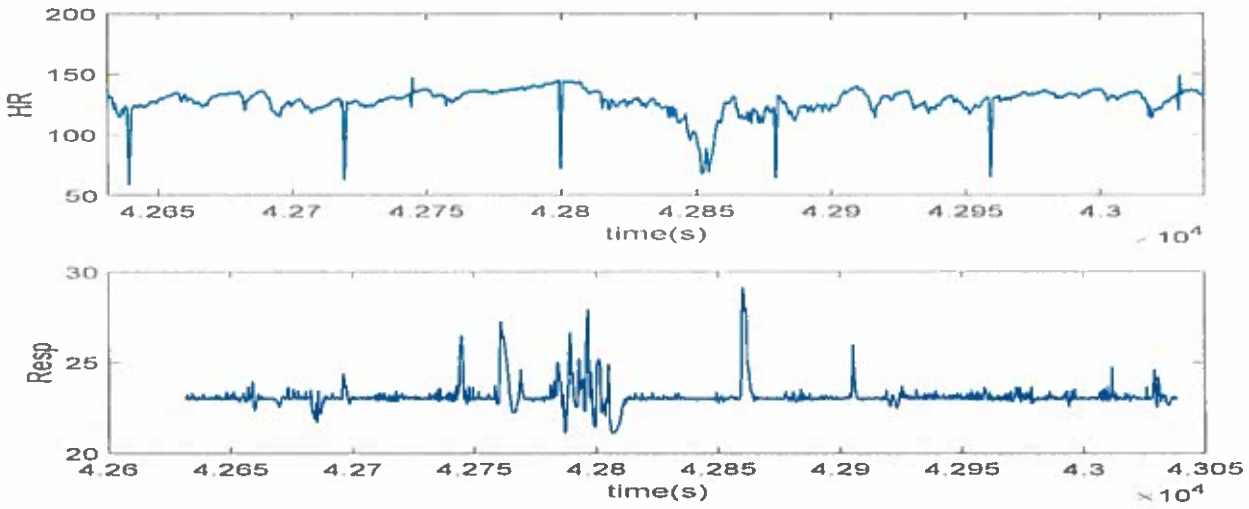

Figure.3 An illustration of a heart rate and respiration interpolation.

3.3 POINT PROCESS AND BIVARIATE MODELLING OF RR AND RESPIRATION

In adults, frequency domain indices have been confirmed by citing specific frequency ranges of interest. Indic and co [11]. established in their work an identical categorization of frequency ranges for babies. This was established by observing the frequency at which the preterm babies had predominant breathing. (i.e. 1Hz) In that study a better-defined categorization of the respiration range was introduced; Low Frequency 0.01-0.15Hz (LF) together with 3 high frequency range, High Frequency-1 0.15-0.45Hz (HF1), High Frequency-2 0.45-0.7Hz (HF2) and High Frequency-3 0.7-1.5Hz (HF3). Eupneic respiration rhythm in preterm babies is generally known to correspond with the HF3 range. To get our measurements within the frequency domain, we employ a multivariate auto regressive model considering both respiration and the RR as output variables. The extended Yule-Walker equations are solved to get the coefficients of the model, the coherence and gain and auto-spectra are obtained in the frequency domain from these coefficients [11]. In a nut shell, this method gives a good estimation of the linear relationship present between the respiration and the RR, as well as its magnitude along the whole frequency range. Hence, the specific indices for the mentioned frequency ranges can be obtained from the spectral estimates.

3.3.1 POINT PROCESS

Heartbeats are a recurring process in which action potentials from the nervous system dictate the rate of cardiac contractions, respiration is also confirmed to be an influence on cardiac control [19]. Hence, we come up with a bivariate linear regression on the mean of the point process probability density of *(p+q)*-order incorporation both RR and respiration (RP) [18]:

$$\mu_{RR}(t) = a_0(t) + \sum_{k=1}^{p} a_k(t)\, RR_{t-k} + \sum_{k=1}^{q} b_k(t) RP_{t-k} \quad (1)$$

Where $a = \{a_0, \ldots., a_k, \ldots, a_p\}$ represents the estimation vector the RR series, and RR_{t-k} is the time difference between every contraction. $b = \{b_0, \ldots., b_k \ldots b_q\}$ represents the estimation vector for the respiration, whereas RP_{t-k} denotes the respiration signal for the same time period.

This linear regression function gives us the mean peak time of the lognormal sample distribution. It is also important to note that the respiration signal was sampled at the RR interval timings, so that they are synchronized.

The continuous RSA gain can now be evaluated as the transfer function from respiration to RR:

$$H_{12}(\omega, t) = \frac{\sum_{k=1}^{q} b_k(t) z^{-k}\big|_{z=e^{j2\pi f_s}}}{1 - \sum_{k=1}^{p} a_k(t) z^{-k}\big|_{z=e^{j2\pi f_s}}} \quad (2)$$

It is however crucial to note that this continuous RSA gain ($RP \rightarrow RR$) is not a significant stand-alone parameter, so it incorporated with a continuous gain from RR to respiration ($RR \rightarrow RP$) in a closed -loop bivariate model to verify the presence of a significant causal coherence between them. This step is a vital part of the process in confirming the presence of interactivity between both systems in preterm infants [18].

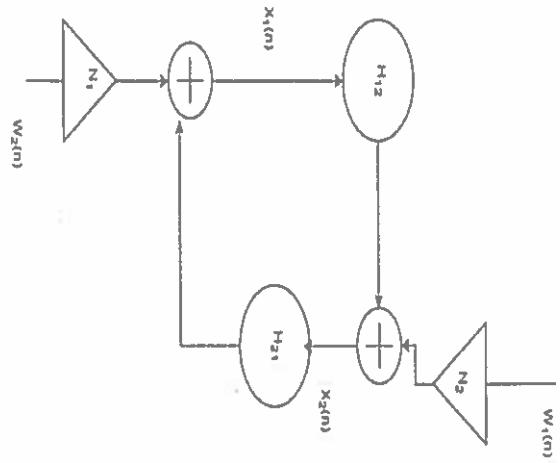

Figure.4 A closed-loop bivariate model, in the figure each block represents a function of the autoregressive coefficients. The H_{12} and H_{21} are transfer functions containing both poles and zeros where as N_1 and N_2 are the all pole parameters that model the input white noises.$X_1(n) = RR$ and $X_2(n) = RP$. The $W_1(n) and\ W_2(n)$ represent white noises[18].

3.3.2 BIVARIATE MODEL

A bivariate autoregressive model shown Figure.4 is represented in the linear system in the discrete-time domain:

$$X(n) = -\sum_{k=1}^{M} A(k) \cdot X(n-k) + w(n) \quad (3)$$

n= 1,2,3....., N

where M is the order it is set at,

N is the total number of points

$$X(n) = [RR(n)\ RP(n)],\ A(k) = \begin{bmatrix} a_{11}(k) & a_{12}(k) \\ a_{21}(k) & a_{22}(k) \end{bmatrix}$$

And

$$w(n) = [\ w_{RR}(n) \quad w_{RP}(n)].$$

w(n) denotes the white noise and a_{ij} denotes the autoregressive coefficients. A recursive algorithm was employed to obtain these coefficients. The spectral components were then obtained from these coefficients. Our model is represented in the frequency domain as;

$$\begin{pmatrix} RR(f) \\ RP(f) \end{pmatrix} = \begin{pmatrix} A_{11}(f) & A_{12}(f) \\ A_{21}(f) & A_{22}(f) \end{pmatrix} \cdot \begin{pmatrix} RR(f) \\ RP(f) \end{pmatrix} + \begin{pmatrix} W_{RR}(f) \\ W_{RP}(f) \end{pmatrix} \quad (4)$$

Where $A_{ij}(f) = \sum_{k=1}^{M} a_{ij}(k) e^{-12\pi fk}$ with I, j = 1,2 and I=$\sqrt{-1}$ which is a complex quantity (2) is expressed as;

$$\begin{pmatrix} RR(f) \\ RP(f) \end{pmatrix} = \begin{pmatrix} H_{11}(f) & H_{12}(f) \\ H_{21}(f) & H_{22}(f) \end{pmatrix} \cdot \begin{pmatrix} W_{RR}(f) \\ W_{RP}(f) \end{pmatrix} \quad (5)$$

Where

$$H_{11}(f) = \frac{1 - A_{22}(f)}{(1 - A_{11}(f))(1 - A_{22}(f)) - A_{21}(f)A_{12}(f)}$$

$$H_{12}(f) = \frac{1 - A_{12}(f)}{(1 - A_{11}(f))(1 - A_{22}(f)) - A_{21}(f)A_{12}(f)}$$

$$H_{21}(f) = \frac{1 - A_{21}(f)}{(1 - A_{11}(f))(1 - A_{22}(f)) - A_{21}(f)A_{12}(f)}$$

$$H_{22}(f) = \frac{1 - A_{11}(f)}{(1 - A_{11}(f))(1 - A_{22}(f)) - A_{21}(f)A_{12}(f)}$$

The coherence γ^2 at a specific frequency id quantified using the traditional definition as:

$$\gamma^2(f) = \frac{|P_{CROSS}(f)|^2}{P_{RR}(f)P_{RP}(f)} \quad (6)$$

Where $P_{RR}(f)$ and $P_{RP}(f)$ are the auto-spectral density functions of RR and RP respectively. $P_{CROSS}(f)$ represents the cross spectral density between RP and RR. The auto-and cross-spectral density functions are estimated:

$$\begin{bmatrix} P_{RR}(f) & P_{CROSS}(f) \\ P_{CROSS}(f) & P_{RP}(f) \end{bmatrix} = \begin{bmatrix} |H_{11}|^2\sigma_{RR}^2 + |H_{12}|^2\sigma_{RP}^2 & H_{11}^*H_{21}\sigma_{RR}^2 + H_{12}^*H_{22}\sigma_{RP}^2 \\ H_{21}^*H_{21}\sigma_{RR}^2 + H_{22}^*H_{12}\sigma_{RP}^2 & |H_{21}|^2\sigma_{RR}^2 + |H_{22}|^2\sigma_{RP}^2 \end{bmatrix} \quad (7)$$

Using Eq. (5) the causal coherence is evaluated with the matching loop regarded as zero, meaning for the causal coherence of respiration influencing RR ($RP \rightarrow RR$), H_{21} is set to zero. For the causal coherence of RR influencing respiration ($RR \rightarrow RP$), H_{12} is then set to zero.

$$\text{Gain } (RP \rightarrow RR) = \left|\frac{H_{12}(f)}{H_{22}(f)}\right| = \left|\frac{A_{12}(f)}{1-A_{11}(f)}\right|$$

$$\text{Gain } (RR \rightarrow RP) = \left|\frac{H_{21}(f)}{H_{11}(f)}\right| = \left|\frac{A_{21}(f)}{1-A_{22}(f)}\right| \quad (8)$$

With both the gain and coherence evaluated along the complete frequency range up to the Nyquist frequency, we then went on to further to calculate the maximum coherence with its matching gain in the various frequency bands mentioned earlier[11].

3.3.3 ACCURACY OF MODELS

We employ the Kolmogorov-Smirnov (KS) statistic to calculate our point process model's goodness-of-fit. Then, time rescaling theorem was used, the theorem mentions that is possible to

transform a point process with an integrable conditional intensity function to a Poisson process with unit rate [16]. As a result, we are then able to measure and discrepancy present between the model and the RR series on a KS plot.

With a 45-degree line signifying an excellent approximation, the KS defines the efficiency of our point process estimation by taking note of the statistical characteristics of the real data. We perform a comparison of area between our approximation and the excellent approximation by considering the farthest deviation distance [19].

We also used an autocorrelation plot of the indices of our model to check to correlation, its purpose was to check if the indices of our model were positively correlated, negative correlated or independent of one another [21].

CHAPTER 4
RESULTS AND DISCUSSIONS

This section comprises of a detailed assessment of the approaches employed in this study. We discuss the experiment protocol, performance of the point process model and the significance of its results, the performance of the bivariate model and a final interpretation of how the results represent cardiorespiratory interactions in the studied subjects.

4.1 EXPERIMENTAL PROTOCOL

To appreciate the characteristics of the cardiorespiratory system, we performed this study in segments. The segments were made up of a bradycardia event, a 10-minute window prior to the event and another 10-minute window after the event. Each segment had two conditions described as: control(10min), Bradycardia event, control(10min). Segments of waveforms with bradycardia were selected, we studied averagely 12 segments per preterm infant. A total of 126 bradycardia events were studied from the 10-infant dataset of the study. Bradycardia was defined to be a heartrate below 100bpm. We then run each selected segment through the point process and later through the bivariate autoregression model to compute the $\mu(t)$ and $\sigma(t)$ indices, coherence and noise variances.

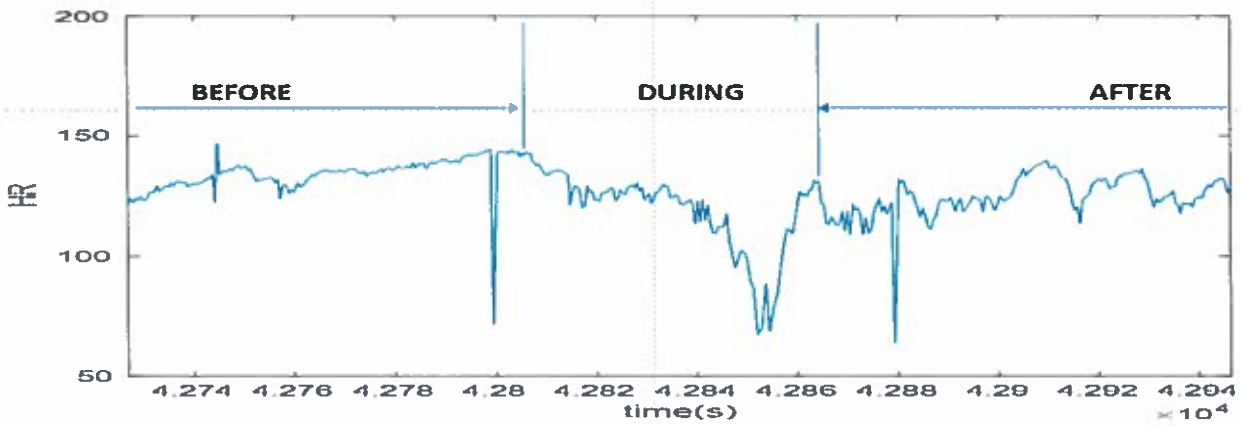

Figure.5 A sample segment of was used throughout study showing a bradycardia event.

4.2 PERFORMANCE OF POINT PROCESS MODEL

The analyzed by the point process model is an interpolated dataset of an infant's RR intervals with its corresponding respiration values. The model is then able to estimate the μ(t) and σ^2(t) indices (i.e. lognormal mean and variance respectively), these indices are evaluated by employing a local maximum-likelihood optimization to attain a continuous approximation of the mean together with the variance of the RR series. This is achieved by setting a history contingent window length of 60 secs for local likelihood to estimate. It's important to note that all μ(t) and σ^2(t) indices evaluated were dependent on the segment being analyzed at the time and that these indices are related to the logarithmic value of the original RR series of that segment. It was observed that for every case of bradycardia the μ(t) and σ^2(t) indices exhibited significant increases respectively. Whilst, the μ(t) followed the RR interval, the σ^2(t) bring to light the distorted fluctuations of RR when a bradycardia event occurs.

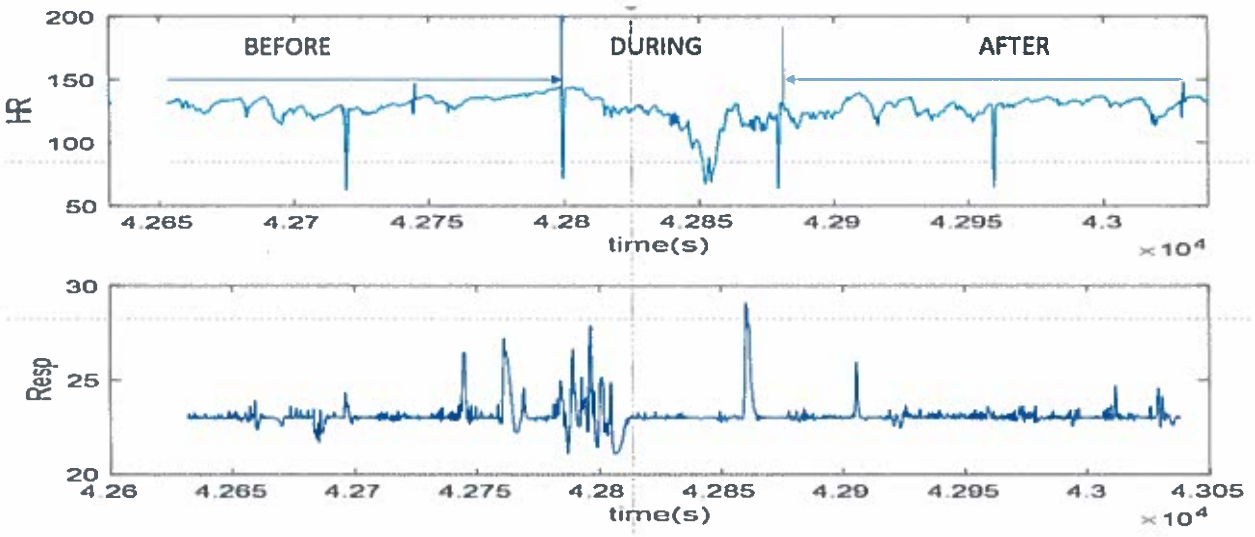

Figure.6 An interpolation of Heartrate and respiration of selected segment with bradycardia.

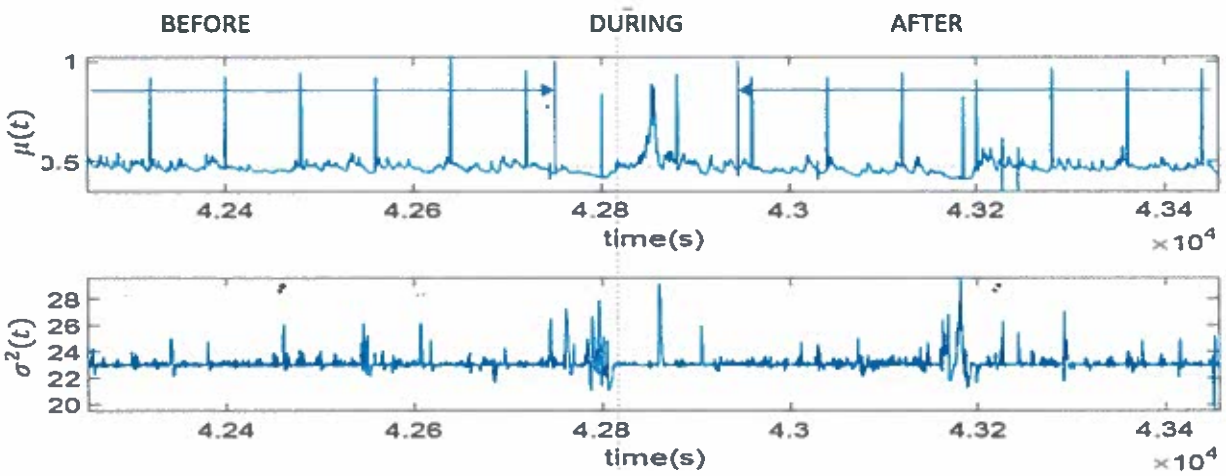

Figure.7 μ(t) and σ^2(t) Indices of the selected segment in Fig.6

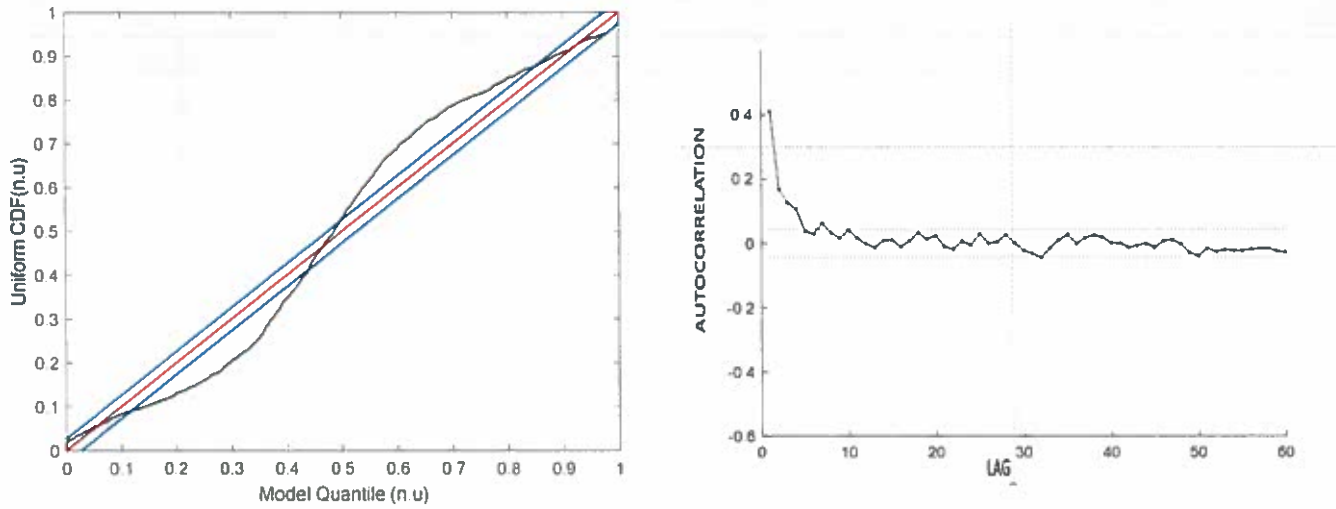

Figure.8 The KS plot autocorrelation plot of the estimation presented in Figure.7

We assessed the point process, lognormal approximation of HRV by examining heartbeats from the selected bradycardia segments taking into considering the respiration information. The select values choices for regression orders of the bivariate model p and q, the max likelihood interval w and weighting time constant α were reached by minimizing the Akaike information criterion for maximum likelihood approximation. This speculative but pragmatic optimization gives $p = 4$, $q = 4, w = 60s, \alpha = .98$.

The KS plot and autocorrelation function for this model are shown in the figure above. The KS plot for this shown segment exhibited a 90% confidence interval of the estimated data from our point process model. This confidence level fluctuated between 90% and 95% depending on the segment under analysis. Such high confidence level achievements could be related to including respiration information in our bivariate model which led to improved estimation. An autocorrelation plot was also used to verify the accuracy of our model.

4.3 PERFORMANCE OF BIVARIATE MODEL

After the point process analysis using data from the selected segments, we approximated the bivariate autoregressive parameters together with the noise variances, to calculate the causal gains, the coherence, and the RP and RR power spectral densities. Also, in each of the defined frequency regions, the maximum coherence together with causal gains at the frequency corresponding the maximum coherence can be computed. However, the causal gains were not computed in this study. Since causal gains are only significant if their matching coherence values are significant. The figures in this section are frequency domain coherence characteristics of a segment with bradycardia events in an infant (i.e. infant 2). The figures are arranged in an order of before bradycardia (10 min control period), bradycardia event, after bradycardia event. After observation of the three defined regions of each studied segment, the classical coherence between the RR and RP increased significantly in the regions where bradycardia occurred. This was noticed across all the studied 126 segments. The classical coherence appeared to return to initial values after the bradycardia event suggesting that there could be both cardiac and respiratory responses that occur during the event and that these responses may be quantifiable. We went on to investigate for a similar trend in the casual coherences (Xcoherence i.e. RP→RR and Ycoherence i.e. RR→RP). Here, in the case of the causal coherence, a surge in coherence during the bradycardia event was recorded in both directions. However, it was observed that just before the onset of bradycardia the Ycoherence (RP→RR) sees a surge and later drops off after the event. This may be interpreted that the respiration increasing above its normal level to keep the heart functioning when the heart rate drops to very low rates. It also observed that the values of coherence in the before segment

and after segments are not widely different meaning the coherence returned toward normal after the bradycardia event.

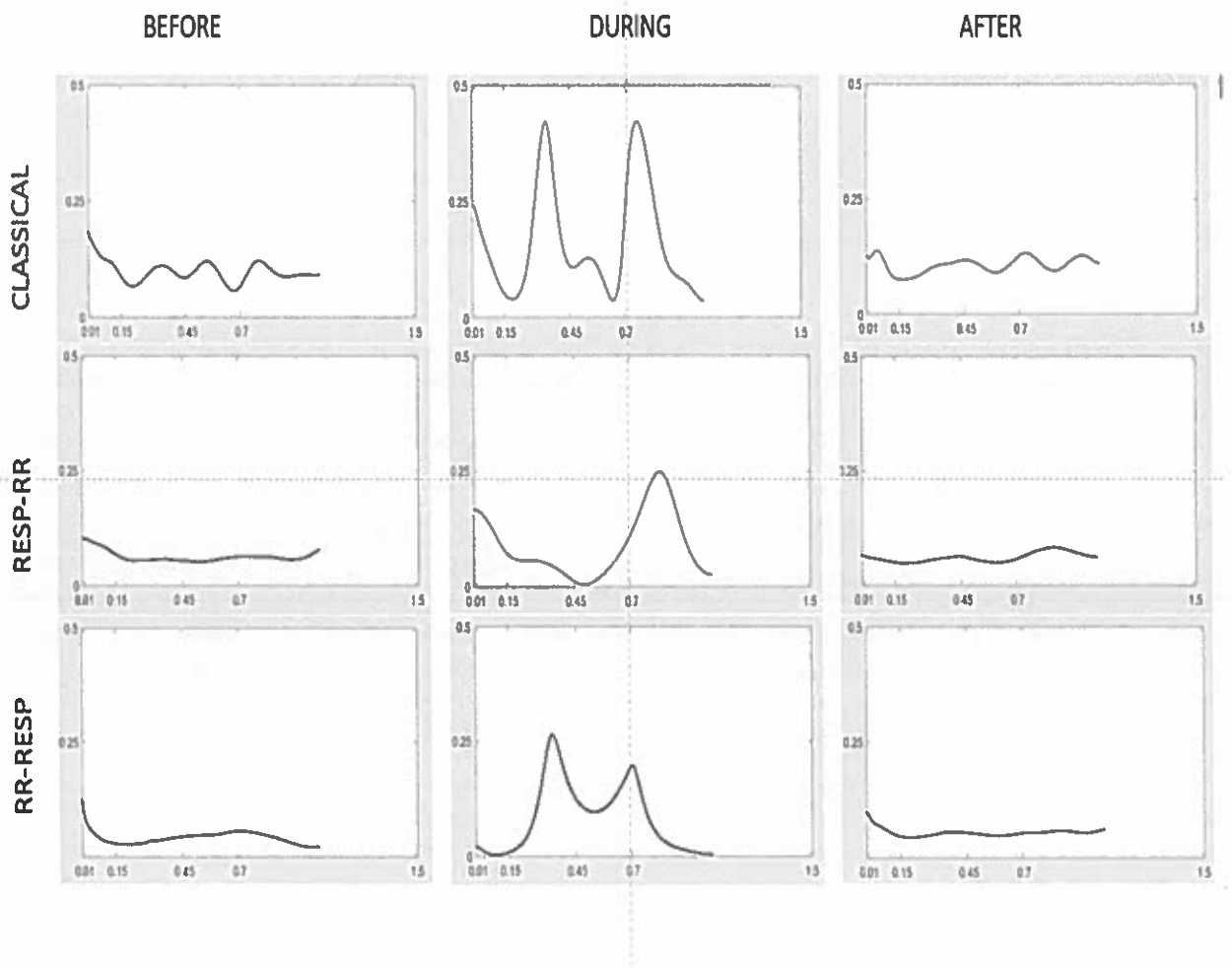

Figure.9 Plots representing coherence during a bradycardia event.

4.4 CARDIO-RESPIRATORY INTERACTIONS

To further grasp the results of our bivariate autoregressive model we perform a statistical analysis of the numerical results. We started by grouping the them just as we have in earlier sections into the 3 groups of before bradycardia, during bradycardia and after bradycardia. This grouping is performed in both classical coherence values and in the causal coherence values as well. An

algorithm is employed to select coherence values only in the defined frequency band within each group (i.e. before bradycardia, during bradycardia and after bradycardia), this is performed on each studied segment. These coherence values in their respective frequency bands are averaged and compared against other mean coherence values from the other frequency bands. This was done to establish significant variability from band to band. It was observed through all 3 groups that the coherence significantly surged during the bradycardia event. An observation (RP→RR) coherence is that the HF3 coherence is significantly different from the other frequency band coherences in this group. Also, in the (RR→RP) coherence the LF band exhibited significant difference from the other frequency bands.

This could be interpreted as the heart trying urge respiration on in an event of bradycardia since this a heart rate dominant band. Conversely, in the HF3 band which is the respiration dominant band, the mean Xcoherence exhibits predominance. This could suggest that the respiration urges the heart on during an event of bradycardia. The results of this analysis suggest that both systems (i.e. cardiac system and respiratory system) work together even during a bradycardia event. **NB:** Low Frequency 0.01-0.15Hz (LF), High Frequency-1 0.15-0.45Hz (HF1), High Frequency-2 0.45-0.7Hz (HF2) and High Frequency-3 0.7-1.5Hz (HF3).

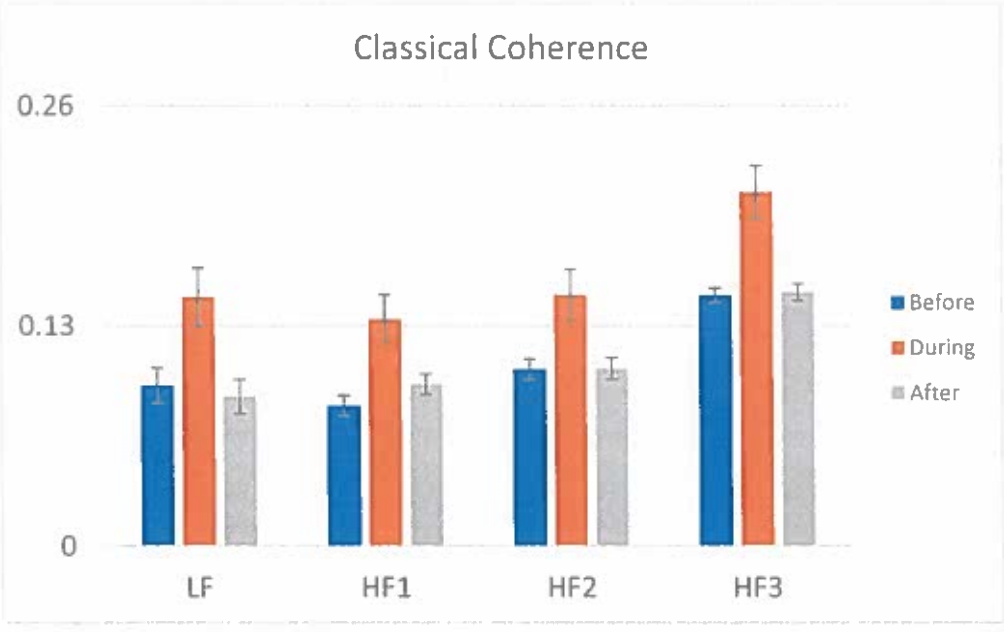

Figure.10 Average power spectral density measures calculated for 10 preterm infants Before bradycardia, During bradycardia and After bradycardia conditions. Coherence during bradycardia significantly higher compared to before and after the event.

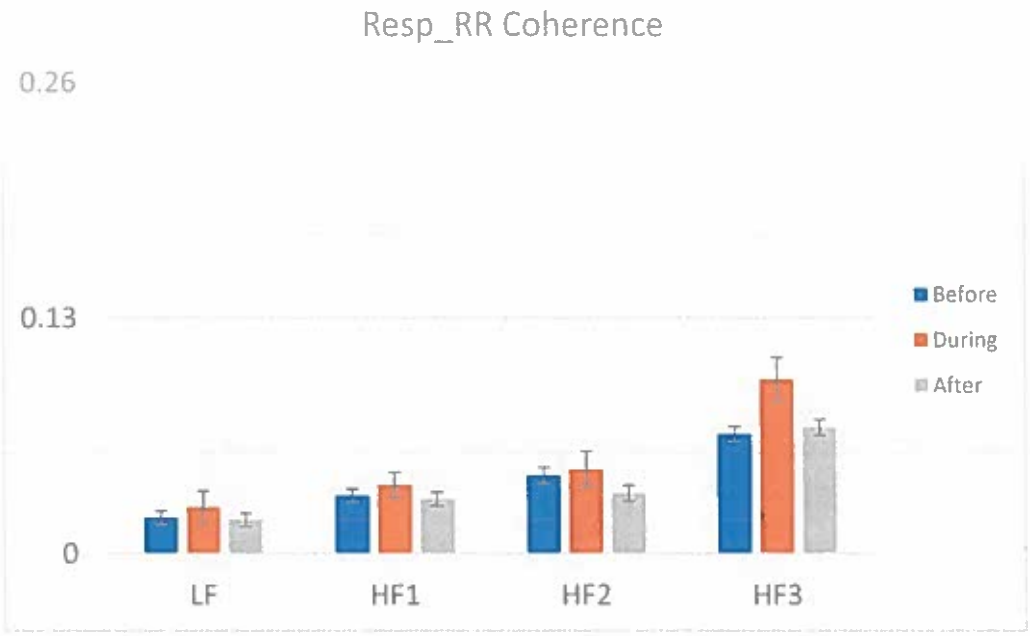

Figure.11 RP→RR causal coherence values of each of the 10 preterm infants. In this case, only the coherence during bradycardia event in the HF3 range is significantly higher suggesting significant interactions from respiration RP to RR.

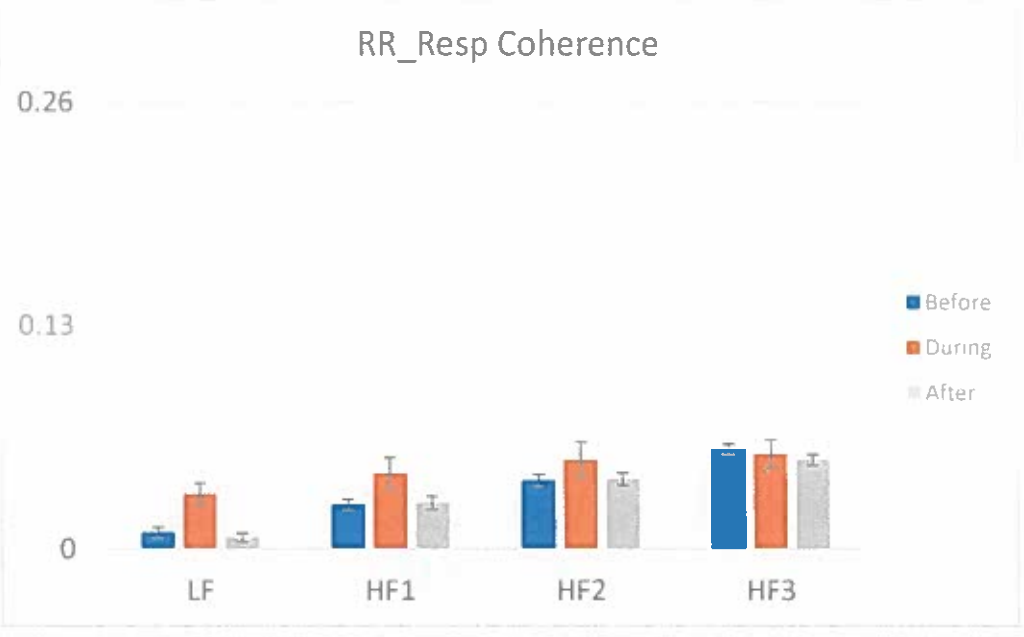

Figure.12 RR→RP causal coherence values of each of the 10 preterm infants. The coherence during bradycardia in the LF range, which corresponds to the RR frequency of the infant, is significantly higher suggesting significant interactions from RR to respiration.

CHAPTER 5
CONCLUSIONS AND LIMITATIONS

We confirmed the presence cardio-respiratory coupling patterns in preterm infants by identifying a noteworthy value of coherence using our point process and bivariate analysis model. This method is derived from series of mathematical tools that have proven to be outstanding in measuring vital cardiovascular control operations in the adult human being, in a ploy to capture a better understanding of the cardiovascular system.

Contrary to the traditional spectral approaches, our approach looks at both the RR and respiratory signal in a single modeling scheme, thus producing frequency quantities in an efficient way. The bivariate algorithm allows to separate the causal interactivity present between the respiration and RR as counter to the other traditional spectral approaches where this interactivity is considered to be unidirectional. Our bivariate model presents a much more relatable linear model of respiration and RR which in turn makes it possible to measure the liaison with the transfer function method and simultaneously to present the heart rate variations as a define amount of oscillatory dynamics which could be related to other physiological rhythms, namely the respiratory cycle.

We then went on to assess the frequency domain characteristics by carrying out a bivariate assessment of respiration and RR employing a multivariate autoregressive approach. It was observed that in the HF3 frequency band (also known to be the respiratory frequency range), that coherence was noticeably high compared to the other frequency bands. These findings do indicate the existence of RSA in preterm babies. This is crucial because this was attained by not only restricting this study to segments with regular heart rate but also those segments with bradycardia which usually are accompanied with a stint of apnea. All of this was done without any filtering methods which could have influenced the detection process.

The closed-loop causal structure we employed measures features which are not particularly detectable by other standard approaches in quantifying heart rate variability, it also permits the separation of the interactivity between the respiration and RR which takes place in both directions and this is indicated in the noticeable causal coherence values. Exceptionally a significant number of the studied segments demonstrated a high coherence value from RP to RR in the HF3 band and

conversely a high number of the segments also demonstrated high values of coherence from RR to RP in the LF band. The significant power percentage observed in the LF band can related to the pause in breathing for before the onset of bradycardia (i.e. Apnea).it is however also important to state that some rather slow respiratory frequencies were observed in the HF3 band, which also might have contributed to the powers observed in the LF band. The reason for these respiratory fluctuations in the LF band is unknown. There have been several suggested causes for such irregularities in the respiration of neonates [22–24]. These suggested factors consist of an elevated loop gain of chemical reactions [25], inconsistencies arising from inherent nonlinear characteristics of the central respiratory oscillator [11], etc. The observation that there is a bidirectional interactivity between respiration and HRV introduces the idea that variations in cardiac dynamics could be a significant reason for the pathological irregularities in respiration (eg. Apnea). We conclude that in the LF band the cardiac system increases its performance to aid the respiratory system where as in the HF3 band, the respiratory system increases performance to aid the cardiac system during the event of bradycardia. Cardio respiratory interactions occur in both directions in case of a life-threatening event (eg. bradycardia) in preterm infants.

Even though it is evident that these low frequency fluctuations can be avoided by the use of filters to heighten the calculational reliability of our employed model, it may also lead to concealing the intrinsic pathological mechanism behind apnea episodes. Thus, all low frequency elements observed in the data are incorporated in our analysis and evaluated the original power distribution whilst sacrificing a minor improvement in the performance of our bivariate model [11]. The merit of our method is that the linear regression described by our method calculates frequency domain values in a prudent manner, and also makes it possible for structuring various oscillations behind cardiovascular control. The bivariate analysis makes it possible to evaluate frequency domain values in the defined frequency bands, namely the LF band, HF1 band, etc.

Significance: We introduced a framework which incorporates a point process model and bivariate regressive model to facilitate the bi-directional analysis of cardio-respiratory interactions. Our technique warrants the analysis of respiration to RR interactions as well the RR to respiration interactions, thus, capturing profound physiological characteristics of the cardiovascular system.

Broader Impact: The proposed framework in this study could be adapted and employed in the analysis of other systems even in adults. The exhaustive method of analysis employed by this

framework makes it a suggested technique in analyzing conditions such as asthma (affects the respiratory system) and other conditions that may affect other systems.

Intellectual Merits: This study adopts and integrates advance signal processing methods to solve an important clinical issue. A better understanding of cardio-respiratory interactions gives a better understanding of the physiological make-up of the cardiovascular system of a preterm infant. Hence, the NICU physician is able to make a better judgment on the developmental progress of a preterm infant.

Limitations: A limitation of our technique is that the bivariate model used is applicable to stationary and quasi-stationary data sets, hence the assumption that every segment we analyzed satisfied that standard. Yet, there are non-stationary episodes in these analyzed segments which could have risen from apnea, hence distorting the stationary state of the respiration signals. In an under-developed system like a preterm infant, both the respiratory and cardiovascular processes may introduce transient interactivity, but because of the susceptibilities of these systems, such interactivity erratic. So, to grasps a better understanding of fast changes a time varying model is required.

An additional limitation is that only bradycardia episodes have been considered in this study, a review considering other life-threatening events (eg. Hypoxemia, Apnea, etc.) to further confirm our findings. The dataset comprising of 10 preterm infants may prove to a small dataset hence for future studies we propose a larger dataset to further confirm out findings. Lastly, other physiological signals such as movement, oxygen saturation could be included as covariates in future studies.

Table 1. Abbreviations

NICU	Neonatal Intensive Care Units
BPD	Bronchopulmonary Dysplasia
GA	Gestational Age
bpm	Beats per minute
CPAP	Continuous Positive Airway Pressure
ECMO	Extracorporeal Membrane Oxygenation
ABP	Arterial Blood Pressure
HRV	Heart Rate Variability
IBI	Inter-Breath Interval
RSA	Respiratory Sinus Arrythmia
ECG	Electrocardiogram
EMA	Evolution Map Approach
DAMOCO	Data Analysis with Models of Coupled Oscillators
OSA	Obstructive Sleep Apnea
QPC	Quadratic Phase Coupling
RWB	Real Wavelet Biphase
PPM	Point Process Model
LF	Low Frequency
HF	High Frequency
PI	Pulse Interval
PICS	Preterm Infants Cardio-Respiratory Signal

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